REMARKS

Priority Claim:

The Examiner has noted that if the benefit of priority of an earlier filed application is desired, then the specification must contain a specific reference to the prior applications in the first sentence of the specification (37 CFR 1.78). Applicants hereby claim the benefit of priority under 35 U.S.C. § 120 to copending U.S. Patent Application Serial No. 09/250,370, filed February 16, 1999, which claims the benefit of priority under 35 U.S.C. § 120 to PCT Application Serial No. PCT/EP 98/05100, filed August 12, 1998, which designates the United States and which claims priority from European Application No. EP 97810567.4, filed August 14, 1997. The requisite specific reference to the prior applications has been amended into the first line of the instant specification.

Specification:

The Examiner has stated that the specification uses the trademark "Bone Protein" and has requested that it be capitalized wherever it appears and that it be accompanied by the generic terminology. Applicants note that Bone Protein is not a trademark (i.e., not an identification of the source or origin of a product), but rather, this term is used in the specification, as capitalized above or as abbreviated to "BP", to reference a partially-purified protein mixture from bovine long bones as described in Poser and Benedict, WO 95/13767 (see page 27, lines 11-15), and which can be produced by a process described in U.S. Patent No. 5,290,763 (see page 29, lines 15-20). It is believed that the specification capitalizes the name whenever it appears and that generic terminology describing the composition is used in the specification.

Claim Objections:

The Examiner has objected to Claims 9 and 33, contending that in Claim 9, "insulin growth factor" should be changed to "insulin-like growth factor" and in Claim 33, "mensical" should be changed to "meniscal". Applicants thank the Examiner for noting these clerical errors. The claims have been amended as suggested.

The Examiner has also objected to Claims 14 and 15, contending that it is improper to incorporate into a claim a reference to a table. To expedite prosecution, Claims 14 and 15 have been canceled without prejudice to or disclaimer of the subject matter therein.

Claim Amendments:

Support for most of the claim amendments is addressed below in the discussion of specific rejections. Support for the amendment in Claim 1 to recite "the quantity of said TGFβ1 in said mixture is greater than 1% of total proteins in said mixture" is found in the specification on page 17, lines 9-13; page 23, line 5 to page 24, line 10; page 31, lines 20-22; and Table 7 (page 81). Support for new Claim 41 is found on page 12, lines 10-11, for example. Support for new Claim 43 is found in Table 7 (page 81).

Objection to the Specification and Rejection of Claim 12 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claim 12, under 35 U.S.C. § 112, first paragraph, contending that this claim is not enabled for the product "Bone Protein". Specifically, the Examiner states that the specification discloses that Bone Protein can be purchased from Sulzer Orthopedics Biologics and is a naturally derived mixture of proteins isolated from demineralized bovine bones and has osteogenic activity *in vivo* and *in vitro*, but the Examiner asserts that the specification does not describe if the bovine bones are fetal, newborn or adult, or how to make Bone Protein (e.g., were the bones demineralized, was an extraction process used, etc.). Therefore, the Examiner contends that the specification is not enabling for a composition comprising Bone Protein.

Applicants traverse the rejection of Claim 12 under 35 U.S.C. § 112, first paragraph. Contrary to the Examiner's assertion that the specification does not teach how to make Bone Protein, Applicants submit that the specification clearly describes what is Bone Protein (BP) and how to make the composition. First, as described on page 27, lines 11-15, Bone Protein is defined as a partially-purified protein mixture from bovine long bones as described in Poser and Benedict, WO 95/13767. In order to expedite prosecution, Applicants have amended the specification to include the incorporated material regarding the mixture as described in WO 95/13767. Specifically, the description of production of the bone growth factor from WO 95/13767 as set forth on page 19, lines 7-22 of WO 95/13767 has been amended into the present specification, in connection with the requirements of MPEP 608.01(p). It is noted that this incorporated material references U.S. Application Serial No. 07/689,459, which is now issued as U.S. Patent No. 5,290,763. Referring to page 29, lines 15-20 of the present specification, it is noted that the specification clearly states that

"one method for producing Bone Protein according to the present invention, and as described, for example, in U.S. Patent No. 5,290,763, entitled "Osteoinductive Protein Mixtures and Purification Processes", incorporated herein by reference in its entirety, typically includes the steps of conducting anion exchange chromatography on a demineralized bone extract solution, a cation exchange procedure, and reverse phase HPLC procedure." Incorporation by reference of essential material in an issued U.S. patent is allowed, pursuant to MPEP 608.01(p). Therefore, it is submitted that the present specification describes in detail how to make Bone Protein such that one of skill in the art would be able to reproducibly make this specific composition using the guidance in the specification.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claim 12 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1-38 Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has made several rejections of the claims under 35 U.S.C. § 112, second paragraph, as follows.

Claims 1, 2, 3, 24, 25, 26, 37 and 38 have been rejected on the basis that the phrase "composition associated with said matrix" is allegedly unclear as to what type of association is intended.

Applicants have amended Claims 1-3, 24-26, 37 and 38 to more clearly describe what is meant by association of the composition with the matrix. In lieu of the phrase "associated with", Applicants have inserted "contained on or within". Support for this amendment is found on page 13, lines 14-18. In addition, the Examples section of the specification provides multiple examples of associating the composition with the matrix.

Claims 2, 25, 26, and 37 have been rejected, because it is allegedly unclear what type of derivation is intended by the phrase "a bone-derived osteogenic or chondrogenic formulation", and it is allegedly unclear how the osteogenic formulation is distinguished from the chondrogenic formulation.

Applicants traverse this rejection and respectfully refer the Examiner to page 28, line 10, to page 29, line 20. This portion of the specification describes that:

"a 'bone-derived osteogenic or chondrogenic formulation' refers to any mixture of proteins containing a complex mixture of proteins which is isolated, or derived, (e.g., by at least one, and typically, multiple purification steps) from a starting material of bone, and which is osteogenic or chondrogenic *in vivo*. A bone-derived osteogenic or chondrogenic formulation contains at least one bone morphogenetic protein (BMP) and the ratio of exogenous TGFβ to the BMP (or more than one BMP) in the mixture is greater than about 10:1. The BMP protein can include any BMP protein, including, but not limited to, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, BMP-8, BMP-9, CDMP, and mixtures thereof. Preferably, the bone-derived formulation is capable of inducing bone and/or cartilage formation in an *in vivo* rat subcutaneous assay such as that described in the Examples section of the Rosen modified Sampath-Reddi rodent assay (Sampath et al., *Proc. Nat'l Acad. Sci. USA*, **80**(21):6591-5 (1983)). More preferably, the bone-derived formulation is capable of inducing a bone score of at least about 1.0 when used at a concentration of at least about 10 μg per 6.5-7.3 mg of bovine tendon collagen in a rat subcutaneous assay as set forth in Example 10 using a bone grading scale set forth in Table 8 (Example 10), and/or induces a cartilage score of at least about 1.0 under the same conditions, using a cartilage grading scale set forth in Table 9 (Example 10)."

The specification then goes on to describe more specifically how one can produce a bone-derived osteogenic or chondrogenic formulation and includes reference to several U.S. Patents and PCT publications that describe particular bone-derived formulations. Therefore, it is clear what is meant by the phrase "a bone-derived osteogenic or chondrogenic formulation". With regard to the terms "osteogenic" and "chondrogenic", it is submitted that these are well known terms in the art and simply refer to the ability of a composition to induce bone growth or cartilage growth, respectively. With regard to the use of these terms in Claims 2, 25, 26, and 37, it is submitted that it is not necessary to distinguish between the terms to practice the invention as claimed, since based on the teachings in the present application, when combined with an exogenous source of TGFβ as taught in the present specification, an osteogenic formulation can become a chondrogenic composition.

Claims 2, 3, 19, 25, 26 and 31 have been rejected, because the Examiner contends that it is unclear if the exogenous TGFβ is ten-fold greater than one BMP or if the exogenous TGFβ is ten-fold greater than the total amount of BMPs if more than one BMP is in the composition.

To clarify this issue, Claims 2, 3, 19, 25, 26 and 31 have been amended to recite that the ratio is established with regard to the total BMPs in the composition if more than one BMP is present. The specification at page 28, lines 10-14, clarifies this issue as well.

Claims 2 and 25 have been rejected as allegedly being indefinite by the term "exogenous". The Examiner states that it is unclear whether the term is relative to the bone in which the formulation is derived or the animal in which the cartilage lesion is repaired. Claims 2 and 25 have been amended to clarify that the TGFβ is exogenous with respect to the bone-derived osteogenic or chondrogenic formulation. As set forth on page 29, line 21, to page 30, line 4:

> "According to the present invention, an "exogenous TGFβ protein" refers to a TGFβ protein that is in substantially pure form and which is not a part of the bone-derived osteogenic or chondrogenic formulation of proteins (i.e., the exogenous TGFβ protein was not isolated from with the bone-derived osteogenic or chondrogenic formulation of proteins). The exogenous TGFβ protein is instead added to the formulation as an additional protein from a different source. It is to be understood that the bone-derived osteogenic or chondrogenic formulation of proteins can contain TGFβ proteins (i.e., "endogenous" proteins), since such mixtures typically do contain at least TGFβ1 and TGFβ2. However, the second component in the composition of exogenous TGFβ protein is intended as a means of increasing the total amount of TGFβ protein in the composition beyond what is naturally found in bone and mixtures derived therefrom."

Claim 3 has been rejected again with regard to the issue of the ratio with respect to the BMP in the formulation. This appears to be an inadvertent reiteration of the rejection of Claims 2, 3, 19, 25, 26 and 31 discussed above, and therefore, the rejection is not addressed again here.

Claim 4 has been rejected on the basis that there is allegedly no antecedent basis for "TGFβ superfamily proteins".

It was not clear to Applicants whether the Examiner was referring to the first or second use of the phrase in the claim, and it was believed that the first use of the phrase provided antecedent basis for the second use, since the first use did not use the definite article "the". However, Claim 4 has been amended in a manner that is believed to address the Examiner's concern.

Claim 11 has been rejected as allegedly being confusing because it is unclear if the TGFβ1, BMP-2, BMP-3 and BMP-7 are in addition to the same components in Claim 1. The Examiner suggests the use of the phrase "further comprising" to clarify the claim.

Applicants have adopted the Examiner's suggestion for amending Claim 11 with respect to Claim 1. However, since this amendment was not suitable given the language in Claims 2 and 3, the reference to Claims 2 and 3 has been removed from Claim 11, and new Claims 39 and 40 have been added to recite the subject matter of Claim 11 with respect to Claims 2 and 3, respectively.

Claim 12 has been rejected on the basis that the term "Bone Protein" is allegedly unclear as to what is Bone Protein. The Examiner further contends that it is unclear if the mixture of proteins further comprises Bone Protein or if the mixture is Bone Protein. With regard to the issue of what is Bone Protein, Applicants refer to the rejection of Claim 12 under 35 U.S.C. § 112, first paragraph, discussed above, and submit that the specification is clear with regard to the identity of Bone Protein. As for whether the mixture of proteins further comprises Bone Protein or is Bone Protein, Applicants submit that the claim does not state that the mixture of proteins consists of Bone Protein and therefore the mixture is not Bone Protein. The claim is clear that the mixture comprises Bone Protein (i.e., can include other components), and indeed, the amounts of TGFβ are recited such that each mixture includes some source of additional TGFβ beyond what would be provided by Bone Protein.

Claims 14 and 15 have been rejected as allegedly being indefinite by the term "about" preceding the scores and Claim 14 is rejected as allegedly being indefinite because it is unclear what characteristics set forth in the recited tables are encompassed in a fractionated score.

To expedite prosecution, and without prejudice to or disclaimer of the subject matter therein, Applicants have cancelled Claims 14 and 15.

Claims 24-26 and 37 have been rejected as allegedly being incomplete. The Examiner asserts that the preamble recites a method for repair of cartilage lesions, yet the only steps recited are implanting and fixing, and so the Examiner believes that it is unclear at which point the lesion is repaired.

Initially, it is noted that the steps of implanting and fixing the product of the present invention result in the repair of the lesion; the repair of the lesion is not something that the artisan does but rather, it occurs naturally as a result of the implantation of the product. Therefore, it is submitted that all of the actual method steps required to achieve repair are present in the method. To clarify this point, a clause has been added to the rejected claims to clarify that the lesion is repaired.

Claim 37 has been rejected because of a period appearing in line 15 and because the phrase "said segmental defect" allegedly lacks antecedent basis.

Claim 37 has been amended to address the Examiner's concerns.

Claim 12 has been rejected as allegedly containing a trademark/trade name by reciting "Bone Protein".

As discussed previously in this response, the term Bone Protein is not a registered trademark but is used in this application as a name to identify a specific composition that is distinguished from other osteogenic or chondrogenic compositions. The specification has clearly defined Bone Protein and therefore, it is believed to be proper to use this phrase in the claim.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-38 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1-8, 10-22 and 24 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1-8, 10-22 and 24 under 35 U.S.C. § 103, contending that these claims are not patentable over Lucas et al. Specifically, the Examiner contends that Lucas et al. teach a formulation comprising a collagen based delivery vehicle, which the Examiner equates with a cartilage repair matrix suitable for conforming to a defect in cartilage, and a cartilage-inducing composition admixed with the repair matrix, wherein the cartilage-inducing composition contains a mixture of proteins extracted from bovine bone. The Examiner asserts that bovine bone intrinsically contains the claim-designated proteins. The Examiner admits that Lucas et al. do not teach the claim designated amounts of the various components of the cartilage-inducing composition, but asserts that since an optimal delivery vehicle would release the inductive proteins at an effective dose over a time period coincident with accumulation of host target cells, it would have been obvious to one of ordinary skill in the art to alter the relative amounts of the components in the cartilage inducing formulation to optimize the delivery and effectiveness of the composition. The Examiner further contends that Lucas et al. teach that the relative amounts of the matrix to protein significantly effects the ability of those products to induce chondrogenesis. Therefore, the Examiner submits that it would have been *prima facie* obvious to the ordinary practitioner to perform routine optimization and arrive at the claimed products.

Applicants traverse the Examiner's rejection of Claims 1-8, 10-22 and 24 under 35 U.S.C. § 103. Initially, Applicants note that for a *prima facie* case of obviousness to be established, the following three basic criteria must be met. First, there must be some suggestion or motivation, either

in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings. Second, there must be a reasonable expectation of success. Third, the combination of references must teach or suggest all of the claim limitations.

Applicants submit that the Lucas et al. reference does not meet all of the above-requirements for a case of *prima facie* obviousness. First, Applicants submit that Lucas et al. do not teach or suggest all of the claim limitations. The Examiner contends that the bone-derived composition of Lucas et al. inherently contains all of the claimed components. However, it is submitted that Lucas et al. do not teach or suggest a composition that includes the amount of TGFβ protein that is recited in each of Claims 1-3. More specifically, Claim 1 comprises an amount of TGFβ1 that exceeds that of the highest determination of the protein in the bone-derived composition, Bone Protein (see Table 7), and Lucas et al. do not teach or suggest modifying the water soluble proteins from bone matrix to increase the amount of any protein, including a TGFβ. Lucas et al. do not teach or suggest producing a composition comprising a bone-derived formulation and any amount of TGFβ that is exogenous to the formulation, as set forth in Claim 2. Moreover, the bone-derived composition of Lucas et al. would not inherently contain the ratio of TGFβ to BMP recited in Claim 3 (i.e., the composition must be manipulated, such as by adding TGFβ, to reach the recited ratio).

The Examiner admits that Lucas et al. do not teach the recited amounts of the proteins in the claims, but contends that to get to the recited amounts of proteins is mere optimization. Applicants traverse the Examiner's position and submit that the present inventors have done extensive testing to determine which combinations of factors are important for achieving cartilage formation that more closely resembles naturally formed cartilage, and have demonstrated in the present application that particular combinations of factors do produce superior cartilage. More specifically, the present inventors have discovered that the combination of *high concentration TGFβ protein* (i.e., beyond that found in bone-derived formulations such as that described by Lucas et al. or found in Bone Protein as described in the present specification) plus osteogenic and/or chondrogenic protein(s) promote cartilage formation in the absence of substantial bone formation, even in a vascularized (permissive bone forming) environment. Applicants submit that the quantities of proteins recited in the claims are *not mere optimization*, but are based on the present inventors discovery of what proteins and what amounts of such proteins lead toward chondrogenesis and away from

osteogenesis, and therefore, the discovery can not be construed to be mere optimization. Indeed, Example 13 and Table 15 show that surprisingly, at high concentrations of TGFβ, the composition of the present invention is primarily chrondrogenic, with very little osteogenic activity observed. Moreover, it is submitted that one of skill in the art would not be able to optimize the water soluble composition of Lucas et al. to arrive at the claimed composition. To optimize a process or composition, one must have knowlege of the variables that effect the result. Lucas et al. do not teach or suggest that a TGFβ protein or any specific protein will have an impact on chondrogenesis; therefore, in the absence of the knowledge that TGFβ is an effective variable, one can not optimize the water soluble proteins of Lucas et al. to arrive at the present invention. Applicants submit that the discovery of the present invention was not a minor tweaking or random changing of components in a natural composition, but involved significant study and manipulation of a composition to achieve superior cartilage growth that has not been previously described. Therefore, it is submitted that even mere optimization of the composition in Lucas et al. would not allow one of ordinary skill in the art to arrive at the claimed composition.

In addition, it is submitted that Lucas et al. do not teach or suggest a matrix that conforms to a defect in cartilage. Lucas et al. teach the implantation of a collagen nodule directly into mouse thigh muscle and therefore, do not teach a matrix that conforms to a defect in cartilage. Moreover, since Lucas et al. is directed to the development of delivery vehicles for *osteogenesis* applications (see page 36, second full paragraph, first sentence), there is no suggestion to make or use a matrix that conforms to a defect in cartilage.

Second, it is submitted that there is not sufficient motivation provided by Lucas et al. or in the knowledge generally available to one of ordinary skill in the art, to modify the reference to arrive at the claimed invention. Although the bovine bone extract described by Lucas et al. is stated to have chondrogenic stimulating activity in an *in vitro* system, the stated goal of Lucas et al. is to develop a delivery vehicle for osteogenesis which contains the inductive proteins sufficient to support the osteogenic cascade *in vivo* (see page 36, second full paragraph). It is noted that Lucas et al. teach that although the collagen/bone protein composition induces "cartilage" in the form of hypertrophic chondrocytes with small amounts of vascular invasion, the formation of cartilage is transient, and is replaced by trabecular bone formation at days 16-25 after implantation (see paragraph bridging pages 30-31). Applicants submit that one of skill in the art *would not be*

motivated to use a composition to induce cartilage growth when the composition has been demonstrated to produce only transient formation of hypertrophic chondrocytes, which quickly leads to *bone formation*. Therefore, taken as a whole, one might be motivated to tweak the composition of Lucas et al. to improve the *osteogenic* activity of the composition, but there is simply not sufficient motivation in Lucas et al. to modify the composition for chondrogenesis or to induce one to use the composition with a matrix that is specifically designed for cartilage repair.

Finally, the teachings of Lucas et al. would not provide one of ordinary skill in the art with a reasonable expectation of success at being able to make and use the claimed composition. As discussed above, the composition of Lucas et al. was not capable of inducing sustainable cartilage growth and arguably, based on the description of the cartilage growth in Lucas et al., this growth would not be considered to be cartilage formation that closely resembles naturally formed cartilage, since only hypertrophic chondrocytes with little vascularization was observed. At best, one would expect the formulation of Lucas et al. to produce bone within a relatively short period of time and therefore would not choose to use such a formulation for cartilage repair, since bone growth in the cartilage lesion is most undesirable.

In contrast, the mixtures of proteins according to the present invention are capable of inducing significant chondrogenesis *in vivo*. This discovery is particularly important for *in vivo* chondrogenesis-induction in a vascular, or bone-forming, environment, and will significantly improve the clinical performance of compositions of the present invention in such *in vivo* environments. Lucas et al. simply do not teach or suggest a composition having this capability, nor a method of repairing cartilage lesions, and do not provide a sufficient motivation or expectation of success to use the composition to attempt to induce cartilage growth or repair. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-8, 10-22 and 24 under 35 U.S.C. § 103.

Rejection of Claims 1-36 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 1-36 under 35 U.S.C. § 103, contending that these claims are not patentable over Li et al., taken with Lucas et al. Specifically, the Examiner contends that Li et al. teach a meniscal augmentation device for implantation into a segmental defect of the meniscus.

The Examiner contends that Li et al. teach that the device can include adhesion molecules and growth factors that could include TGFα, TGFβ, FGF, EFG and PDGF. The Examiner contends that Li et al. also teach a method of repair of cartilage lesions comprising implanting and fixing a product into a lesion. The Examiner admits that Li et al. do not teach the claim designated proteins in the claim-designated ratios, but submits that Lucas et al. teach a product comprising a collagen based delivery vehicle and a cartilage-inducing composition of proteins extracted from bovine bone. The Examiner asserts that Lucas et al. teach ectopic cartilage formation as a result of implanting the composition. The Examiner again asserts that although Lucas et al. do not teach the claim-designated amounts of the proteins, it would be routine optimization to arrive at the claimed composition, as one would allegedly alter the amounts to optimize delivery and effectiveness of the components at the lesion. The Examiner contends that the motivation to use the protein composition of Lucas et al. in the device of Li et al. is provided because Lucas et al. allegedly clearly demonstrate that the composition effectively induces cartilage at the site of implantation. Therefore, the Examiner submits that the invention is *prima facie* obvious in view of the combination of Li et al. and Lucas et al.

Applicants traverse the Examiner's rejection of Claims 1-36 under 35 U.S.C. § 103. Applicants refer to the discussion of Lucas et al. above and reiterate that Lucas et al. do not teach or suggest a composition that includes the amount of TGFβ protein that is recited in each of Claims 1-3, 24-26 or 37 (or dependents therefrom), nor does this reference provide the motivation or expectation of success at modifying the composition for the purpose of inducing cartilage growth or repairing cartilage lesions. As discussed in some detail above, contrary to the Examiner's assertion, Lucas et al. do not demonstrate that the composition disclosed in that reference effectively induces cartilage at the site of implantation. Therefore, even if the reference is combined with Li et al., the combination fails to teach or suggest the present invention or provide the motivation to modify the combination of references to arrive at the present invention.

With regard to Li et al., this reference discloses a meniscal augmentation device which has characteristics shared with the cartilage repair matrix component of the claimed cartilage repair product. However, Li et al. do not teach or suggest the use of any bone morphogenetic proteins or bone matrix proteins, nor specifically the use of the presently claimed mixtures of proteins. Li et al. merely note that one or more growth factors may be used to aid in meniscal tissue generation, but

Li et al. do not describe any particular combinations of factors, do not provide any teachings regarding quantities of factors, and do not provide any prophetic or working examples showing the use of any factors with a meniscal augmentation device. Therefore, Li et al. lacks sufficient teachings or motivation to be combined with Lucas et al. and even if the references are combined, as discussed above, the combination fails to teach or suggest the claimed invention.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-36 under 35 U.S.C. § 103.

Rejection of Claims 37-38 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 37-38 under 35 U.S.C. § 103, contending that these claims are not patentable over Li et al. taken with Lucas et al. and Stone et al. The Examiner Li et al. and Lucas et al. essentially for the reasons described in the previously discussed rejections. The Examiner admits that Li et al. do not teach using two products as described in Claims 37-38, wherein one product is a sheet form and the other is in the form of a segmental defect. However, the Examiner contends that Stone et al. teach that bonding of a collagenous meniscal implant to lesion edges is more difficult than bonding to the thicker vascular periphery of a lesion and may leave the implant unstable. Therefore, the Examiner asserts that it would have been obvious to provide two repair matrix products in the recited forms to provide a sheet interface between the lesion and the segmental product. The Examiner again contends that the combination of references renders the claimed invention *prima facie* obvious.

Applicants traverse the rejection of Claims 37-38 under 35 U.S.C. § 103. Applicants refer to the discussion regarding the combination of Lucas et al. and Li et al. and submit that the reference of Stone et al. does not make up for the deficiencies Lucas et al. and/or Li et al., even when taken together with these references. The combination of references fails to teach the claimed composition, and additionally fails to provide any motivation to make and modify the combination as the Examiner has done. Moreover, Applicants submit that Stone et al. do not provide any teaching or motivation to provide a two product repair system as recited in Claims 37-38. A teaching that bonding of a meniscal implant to lesion edges is more difficult than bonding to the vascular periphery is hardly a teaching to use a first matrix shaped as a sheet which is implanted between the edge of a lesion and a second matrix shaped to conform to the segmental defect, since

the recognition of a problem does not in itself teach or suggest a resolution to that problem. Therefore, Applicants submit that Stone et al. do not teach or suggest the elements for which the Examiner cites the reference, nor are the elements suggested by the combination of references.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 37-38 under 35 U.S.C. § 103.

Provisional Rejection of Claims 1-38 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting:

The Examiner has rejected Claims 1-38 under the judicially created doctrine of obviousness-type double patenting, contending that these claims are obvious in view of copending U.S. Application Serial No. 09/250,370 in view of Li et al. taken with Lucas et al. The Examiner contends that the claims of the instant application and the copending '370 application are directed to products for cartilage repair comprising matrices and cartilage-inducing compositions and to methods of using the products. The Examiner contends that the claims differ in the recitation of the specific protein components and amounts, but contends that the claims in the present application are not limited to the recited proteins by virtue of the "comprising" transitional phrase. The Examiner asserts that Li et al. and Lucas et al. teach products comprising an admixture of various proteins associated with a repair matrix and that the references teach that the types and amounts of proteins should be optimized to repair cartilage lesions. Therefore, the Examiner contends that it would have been obvious to optimize the protein components of the present claims and of the '370 application claims for the purpose of implanting the products into a cartilage defect.

Applicants acknowledge that this rejection is a provisional rejection, since the '370 application has not yet issued. Therefore, while Applicants believe that there are non-obvious distinctions between the claims of the '370 application and the present claims, Applicants will defer presenting arguments or alternatively, filing a terminal disclaimer, until all other issues in the present application have been resolved.

Applicants have tried to respond to all of the concerns as set forth by the Examiner in the May 9 Office Action. The Examiner is encouraged to contact the below-named agent at (303) 863-9700 in the event that clarification of Applicants' position is needed.

Respectfully submitted,

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Date: September 10, 2001

Marked-Up Version Showing Amendments

In the Specification:

The following paragraph has been added on page 1, line 3, immediately following the title of the application:

--CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority under 35 U.S.C. § 120 as a continuation-in-part of copending U.S. Patent Application Serial No. 09/250,370, filed February 16, 1999, and entitled "Device and Method for Regeneration and Repair of Cartilage Lesions", which is a continuation-in-part under 35 U.S.C. § 120 of PCT Application No. PCT/EP 98/05100, entitled "Composition and Device for In Vivo Cartilage Repair Comprising Nanocapsules with Osteoinductive And/or Chondroinductive Factors", filed August 12, 1998, which designates the United States and which claims priority from European Application No. EP 97810567.4, entitled "Composition and Device for In Vivo Cartilage Repair", filed August 14, 1997. Each of the above-identified applications is incorporated herein by reference in their entireties.--

The single paragraph on page 27, spanning lines 7-27, has been amended as follows to form two paragraphs.

--In one aspect of this embodiment of the present invention, a mixture of proteins suitable for use in a chondrogenesis-inducing composition portion of a cartilage repair product of the present invention includes the following proteins: TGFβ1, TGFβ2, TGFβ3, BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, CDMP, FGF-I, osteocalcin, osteonectin, BSP, lysyloxidase, cathepsin L pre, albumin, transferrin, Apo A1 LP and Factor XIIIb. In yet another embodiment, a suitable mixture of chondrogenesis-enhancing proteins includes the mixture of proteins referred to herein as Bone Protein (BP), which is defined herein as a partially-purified protein mixture from bovine long bones as described in Poser and Benedict, WO 95/13767, incorporated herein by reference in its entirety. As described in Poser and Benedict, WO 95/13767: "Bone growth factor was isolated from the

cortical diaphyses of bovine long bones. The marrow and soft tissue was cleaned from the long bones, and the bones were pulverized and demineralized in 1.0 normal (N) hydrochloric acid at a 1:13 weight to volume ratio for 16 hours at 25°C. The bone particles were washed in distilled water and then extracted in a buffered solution comprising of 4 N guanidine hydrochloride buffered with 0.1 N Tris, pH 7.6 at a concentration of 3 milliliters of buffered solution per gram of original powdered bone. The bone was extracted for 48 h at 15°C. The extracted bone particles were then passed through a series of chromatographic purification steps as described in U.S. Application Serial No. 07/689,459 to extract bone growth factor having bone inductive effect at doses less than 35 microgram (μg)."

In another aspect of this embodiment of the present invention, the cartilage inducing composition has an identifying characteristic selected from the group consisting of an ability to induce cellular infiltration, an ability to induce cellular proliferation, an ability to induce angiogenesis, and an ability to induce cellular differentiation to type II collagen-producing chondrocytes. In yet another aspect of this embodiment of the present invention, the mixture of proteins, when used at a concentration of at least about 10 μg per 6.5-7.3 mg of bovine tendon collagen in a rat subcutaneous assay, induces a bone score of from about 1.0 to about 3.5, using a bone grading scale set forth in Table 8 (Example 10), and induces a cartilage score of at least about 1.2, using a cartilage grading scale set forth in Table 9 (Example 10). A rat subcutaneous assay suitable for determining bone and cartilage scores according to this aspect, and the grading scales of Tables 8 and 9 are described in detail in the Examples Section.--

In the Claims:

Claims 14 and 15 have been canceled.

Claims 1-11, 19, 24-26, 31, 33, 37 and 38 have been amended as shown below.

Claims 12, 13, 16-18, 20-23, 27-30, 32 and 34-36 are have not been changed.

Claims 39-43 have been added.

39. (Once Amended) A product for repair of cartilage lesions, comprising:

a. a cartilage repair matrix suitable for conforming to a defect in cartilage; and

b. a cartilage-inducing composition [associated with] contained on or within said matrix comprising a mixture of proteins comprising: transforming growth factor β1 (TGFβ1), bone morphogenetic protein (BMP)-2, BMP-3, and BMP-7;

wherein the quantity of said TGFβ1 in said mixture is greater than 1% [from about 0.01% to about 99.99%] of total proteins in said mixture;

wherein the quantity of said BMP-2 in said mixture is from about 0.01% to about 10% of total proteins in said mixture;

wherein the quantity of said BMP-3 in said mixture is from about 0.1% to about 15% of total proteins in said mixture; and,

wherein the quantity of said BMP-7 in said mixture is from about 0.01% to about 10% of total proteins in said mixture.

40. (Once Amended) A product for repair of cartilage lesions, comprising:

a. a cartilage repair matrix; and

b. a cartilage-inducing composition [associated with] contained on or within said matrix comprising a mixture of proteins comprising:

(i) a bone-derived osteogenic or chondrogenic formulation containing at least one bone morphogenetic protein (BMP); and,

(ii) [an exogenous] a TGFβ protein that is exogenous to said formulation of (i);

wherein the ratio of said exogenous TGFβ protein to [said at least one] total BMP in said mixture of proteins is greater than about 10:1; and,

wherein said exogenous TGFβ protein is present in an amount sufficient to increase cartilage induction by said composition over a level of cartilage induction

by said bone-derived osteogenic or chondrogenic protein formulation in the absence of said exogenous TGFβ protein.

41. (Once Amended) A product for repair of cartilage lesions, comprising:

a. a cartilage repair matrix; and

b. a cartilage-inducing composition [associated with] contained on or within said matrix comprising a mixture of proteins comprising:

(i) a TGFβ protein; and,

(ii) at least one bone morphogenetic protein (BMP);

wherein the ratio of said TGFβ protein to [said] total BMP [protein] in said mixture of proteins is greater than about 10:1.

42. (Once Amended) The product of [any one of Claims 1,] Claim 2[, or 3], wherein said mixture of proteins comprises TGFβ superfamily proteins consisting of: TGFβ1, bone morphogenetic protein (BMP)-2, BMP-3, and BMP-7, wherein said TGFβ superfamily proteins comprise from about 0.5% to about 99.99% of said mixture of proteins.

43. (Once Amended) The product of any one of Claims [Claim] 4 or 42, wherein said TGFβ superfamily proteins comprise from about 0.5% to about 25% of said mixture of proteins.

44. (Once Amended) The product of any one of Claims [Claim] 4 or 42, wherein the quantity of said TGFβ1 in said mixture is from about 0.01% to about 75% of total proteins in said mixture.

45. (Once Amended) The product of any one of Claims 1, [Claim] 4 or 42, wherein the quantity of said TGFβ1 in said mixture is from about 33% to about 99.99% of total proteins in said mixture.

46. (Once Amended) The product of any one of Claims 1, [Claim] 4 or 42, wherein said mixture of proteins further comprises at least one bone matrix protein selected from the group consisting of osteocalcin, osteonectin, bone sialoprotein (BSP), lysyloxidase,

cathepsin L pre, osteopontin, matrix GLA protein (MGP), biglycan, decorin, proteoglycan-chondroitin sulfate III (PG-CS III), bone acidic glycoprotein (BAG-75), thrombospondin (TSP) and fibronectin; wherein said bone matrix protein comprises from about 20% to about 98% of said mixture of proteins.

47. (Once Amended) The product of any one of Claims 1, [Claim] 4 or 42, wherein said mixture of proteins further comprises at least one growth factor protein selected from the group consisting of fibroblast growth factor-I (FGF-I), FGF-II, FGF-9, leukocyte inhibitory factor (LIF), insulin, insulin-like growth factor I (IGF-I), IGF-II, platelet-derived growth factor AA (PDGF-AA), PDGF-BB, PDGF-AB, stromal derived factor-2 (SDF-2), pituitary thyroid hormone (PTH), growth hormone, hepatocyte growth factor (HGF), epithelial growth factor (EGF), transforming growth factor-α (TGFα) and hedgehog proteins; wherein said growth factor protein comprises from about 0.01% to about 50% of said mixture of proteins.

48. (Once Amended) The product of any one of Claims 1, [Claim] 4 or 42, wherein said composition further comprises one or more serum proteins.

49. (Once Amended) The product of [any one of Claims] Claim 1[, 2 or 3], wherein said mixture of proteins further comprises [TGFβ1,] TGFβ2, TGFβ3, [BMP-2, BMP-3,] BMP-4, BMP-5, BMP-6, [BMP-7,] CDMP, FGF-I, osteocalcin, osteonectin, BSP, lysyloxidase, cathepsin L pre, albumin, transferrin, Apo A1 LP and Factor XIIIb.

19. (Once Amended) The product of any one of Claims 2 or 3, wherein the ratio of said TGFβ protein to [said] total BMP [protein] in said mixture of proteins is greater than about 100:1.

24. (Once Amended) A method for repair of cartilage lesions, comprising implanting and fixing into a cartilage lesion a product comprising:

a. a cartilage repair matrix suitable for conforming to a defect in cartilage; and

b. a cartilage-inducing composition [associated with] contained on or within said matrix comprising a mixture of proteins comprising: transforming growth factor β1 (TGFβ1), bone morphogenetic protein (BMP)-2, BMP-3, and BMP-7;

wherein the quantity of said TGFβ1 in said mixture is greater than 1% [from about 0.01% to about 99.99%] of total proteins in said mixture;

wherein the quantity of said BMP-2 in said mixture is from about 0.01% to about 10% of total proteins in said mixture;

wherein the quantity of said BMP-3 in said mixture is from about 0.1% to about 15% of total proteins in said mixture; and,

wherein the quantity of said BMP-7 in said mixture is from about 0.01% to about 10% of total proteins in said mixture;

whereby implanting and fixing said product into said cartilage lesion enhances repair of said defect in cartilage as compared to in the absence of said product.

25. (Once Amended) A method for repair of cartilage lesions, comprising implanting and fixing into a cartilage lesion a product comprising:

a. a cartilage repair matrix; and,

b. a cartilage-inducing composition [associated with] contained on or within said matrix comprising a mixture of proteins comprising:

(i) a bone-derived osteogenic or chondrogenic formulation of proteins containing at least one bone morphogenetic protein (BMP); and,

(ii) [an exogenous] a TGFβ protein that is exogenous to said formulation of (i);

wherein the ratio of said exogenous TGFβ protein to [said at least one] total BMP in said mixture of proteins is greater than about 10:1; and,

wherein said exogenous TGFβ protein is present in an amount sufficient to increase cartilage induction by said composition over a level of cartilage induction

by said bone-derived osteogenic or chondrogenic protein formulation in the absence of said exogenous TGFβ protein;

whereby implanting and fixing said product into said cartilage lesion enhances repair of said defect in cartilage as compared to in the absence of said product.

26. (Once Amended) A method for repair of cartilage lesions, comprising implanting and fixing into a cartilage lesion a product comprising:

a. a cartilage repair matrix; and,

b. a cartilage-inducing composition [associated with] contained on or within said matrix comprising a mixture of proteins comprising:

(i) a TGFβ protein; and,

(ii) at least one bone morphogenetic protein (BMP);

wherein the ratio of said TGFβ protein to [said] total BMP [protein] in said mixture of proteins is greater than about 10:1;

whereby implanting and fixing said product into said cartilage lesion enhances repair of said defect in cartilage as compared to in the absence of said product.

31. (Once Amended) The method of any one of Claims 25 or 26, wherein the ratio of said TGFβ protein to [said] total BMP [protein] in said mixture of proteins is greater than about 100:1.

33. (Once Amended) The method of any one of Claims 24, 25 or 26, wherein said cartilage lesion is a [mensical] meniscal cartilage lesion.

37. (Once Amended) A method for repair of segmental cartilage lesions, comprising implanting and fixing into a segmental cartilage lesion:

a. a first product comprising:

(i) a cartilage repair matrix configured as a sheet; and

(ii) a cartilage-inducing composition [associated with] contained on or within said matrix comprising a mixture of proteins comprising:

transforming growth factor β1 (TGFβ1), bone morphogenetic protein (BMP)-2, BMP-3, and BMP-7;

wherein the quantity of said TGFβ1 in said mixture is greater than 1% [from about 0.01% to about 99.99%] of total proteins in said mixture;

wherein the quantity of said BMP-2 in said mixture is from about 0.01% to about 10% of total proteins in said mixture;

wherein the quantity of said BMP-3 in said mixture is from about 0.1% to about 15% of total proteins in said mixture; and,

wherein the quantity of said BMP-7 in said mixture is from about 0.01% to about 10% of total proteins in said mixture[.]; and,

b. a second product comprising a cartilage repair matrix configured to replace cartilage removed from [said] a segmental [defect] lesion;

wherein said second product is implanted into said lesion and wherein said first product is implanted between an edge of said lesion and said second product to provide an interface between said lesion and said second product.

38. (Once Amended) The method of Claim 37, wherein said second product further comprises a cartilage-inducing composition [associated with] contained on or within said matrix comprising a mixture of proteins comprising: transforming growth factor β1 (TGFβ1), bone morphogenetic protein (BMP)-2, BMP-3, and BMP-7;

wherein the quantity of said TGFβ1 in said mixture is greater than 1% [from about 0.01% to about 99.99%] of total proteins in said mixture;

wherein the quantity of said BMP-2 in said mixture is from about 0.01% to about 10% of total proteins in said mixture;

wherein the quantity of said BMP-3 in said mixture is from about 0.1% to about 15% of total proteins in said mixture; and,

wherein the quantity of said BMP-7 in said mixture is from about 0.01% to about 10% of total proteins in said mixture.